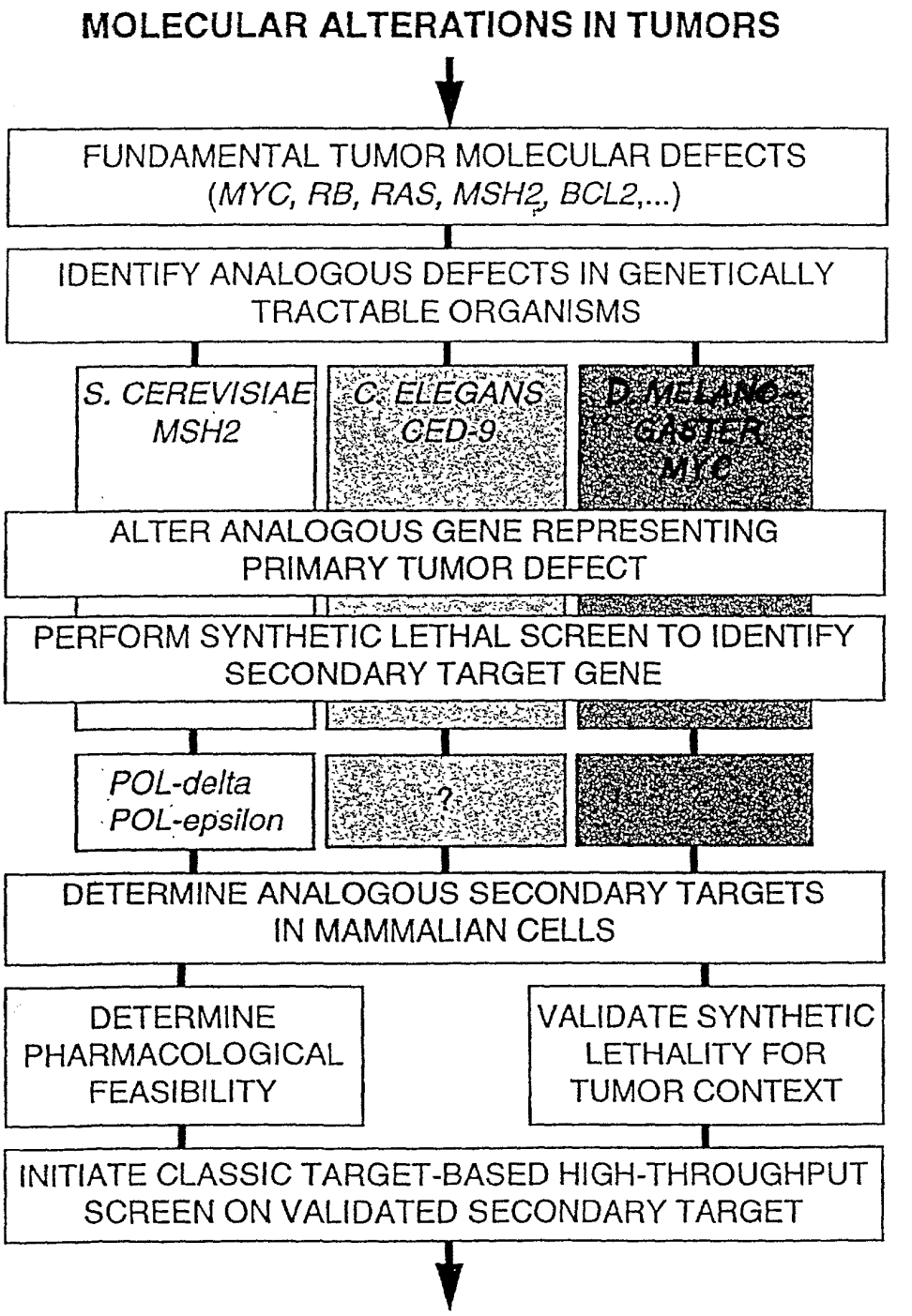
FIGURE 1


MOLECULAR ALTERATIONS IN TUMORS
FUNDAMENTAL TUMOR MOLECULAR DEFECTS
(MYC, RB, RAS, MSH2, BCL2,...)
IDENTIFY ANALOGOUS DEFECTS IN GENETICALLY TRACTABLE ORGANISMS
S. CEREVISIAE MSH2
C. ELEGANS CED-9
D. MELANOGASTER MYC
ALTER ANALOGOUS GENE REPRESENTING PRIMARY TUMOR DEFECT
PERFORM SYNTHETIC LETHAL SCREEN TO IDENTIFY SECONDARY TARGET GENE
POL-delta
POL-epsilon
?
DETERMINE ANALOGOUS SECONDARY TARGETS IN MAMMALIAN CELLS
DETERMINE PHARMACOLOGICAL FEASIBILITY
VALIDATE SYNTHETIC LETHALITY FOR TUMOR CONTEXT
INITIATE CLASSIC TARGET-BASED HIGH-THROUGHPUT SCREEN ON VALIDATED SECONDARY TARGET
ANTI-CANCER DRUGS BASED ON TUMOR CONTEXT

Cell Cycle/DNA Damage Response Pathways

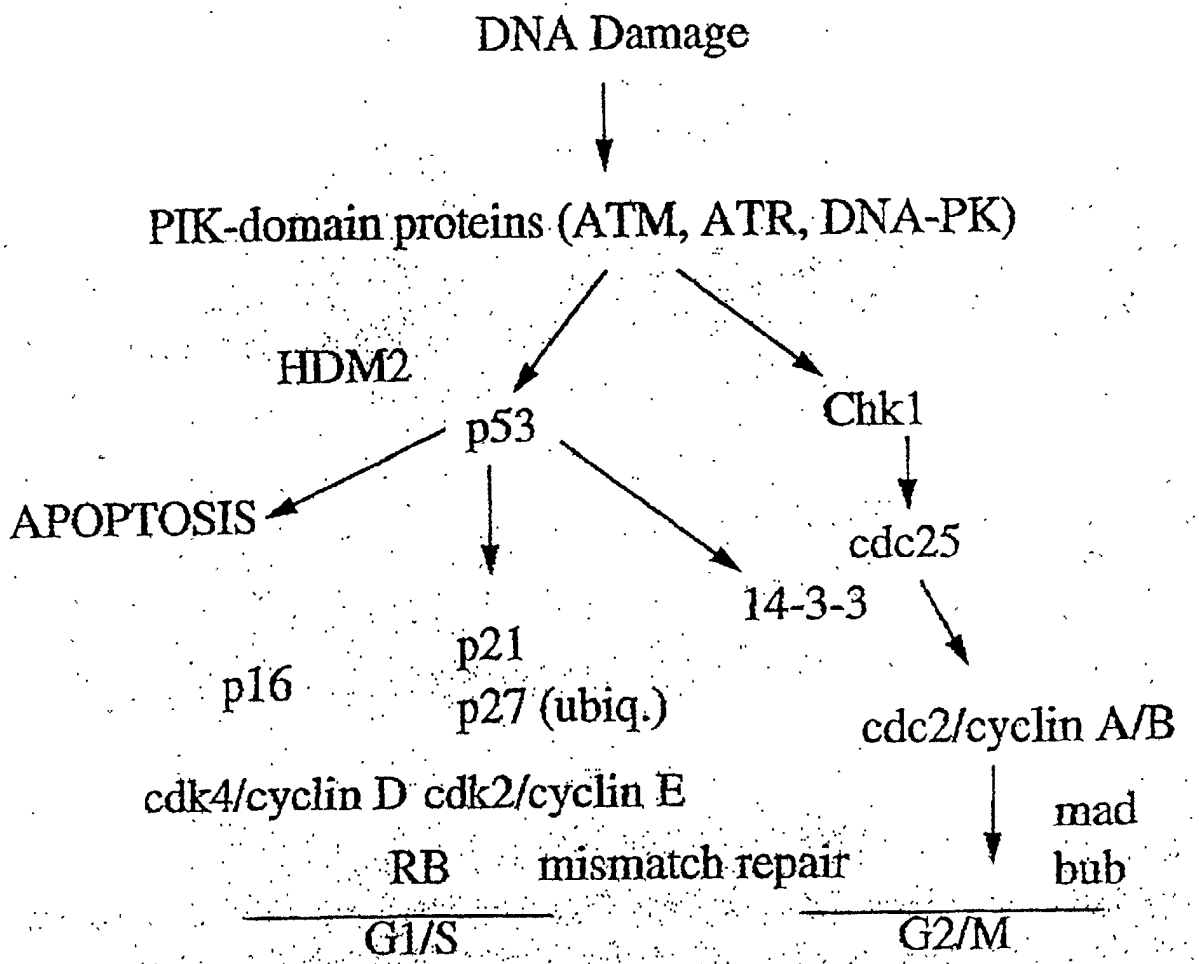
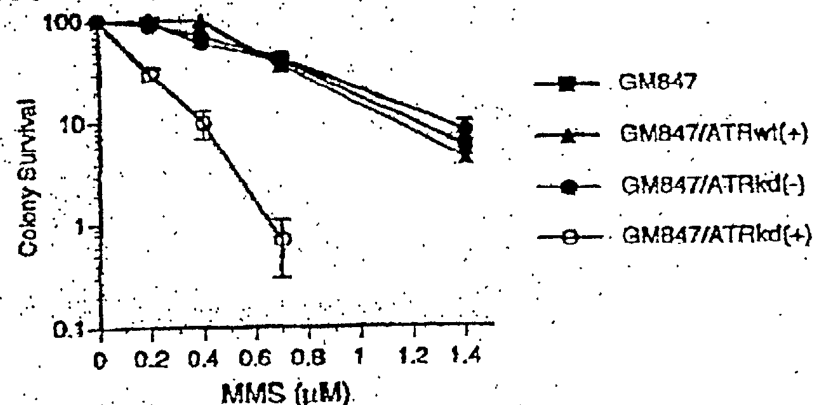


Figure2

MAMMALIAN CELL EVALUATION OF ATR AS A TARGET

1. Overexpression of ATR-KD not tolerated in human tumor cell lines (MCF-7, A549)

2. Inducible ATR-KD sensitizes cells to DNA damaging agents



3. LCK promoter driven ATR-KD transgenic mice have cells stably expressing ATR-KD in thymus

Figure 3

Figure 4

Synthetic lethality:

- Use primary defect as a selective context to kill tumor cells with an alteration in gene A.
- Combined defects in gene A and gene B kill tumor cells while disrupting gene B activity alone has no effect on normal cells.

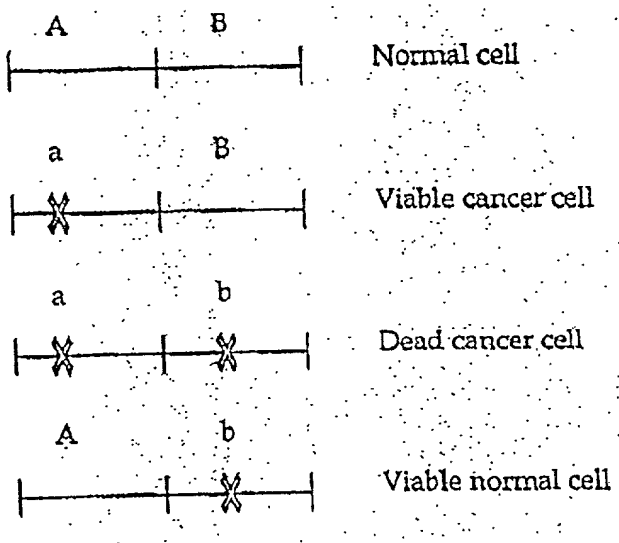


Figure 5

. Human genes altered in tumors and their relatives in model genetic systems. Genes that are not structural homologs but act in analogous pathways (such as human *p53* and *S. cerevisiae RAD9*) are shown in brackets. *Saccharomyces cerevisiae* genes are designated with superscript Sc, *S. pombe* with Sp, *C. elegans* with Ce, and *D. melanogaster* with Dm. Because of space limitations, this is only a representative list of genes mutated in tumors that have genetic analogs in model systems.

Function	Human genes	Model system analogs: structural homologs or related biological roles
DNA damage checkpoint	*p53*	[*RAD9*^{Sc}, *rad1*$^{+Sp}$]
	ATM	*MEC1*^{Sc}, *TEL1*^{Sc}, *rad3*$^{+Sp}$, *mei-41*^{Dm}
DNA mismatch repair	*MSH2*, *MLH1*	*MSH2*^{Sc}, *MLH1*^{Sc}
Nucleotide excision repair	*XP-A*, *XP-B*	*RAD14*^{Sc}, *RAD25*^{Sc}
O^6-methylguanine reversal	*MGMT*	*MGT1*^{Sc}
Double-strand break repair	*BRCA2*, *BRCA1*	[*RAD51*^{Sc}, *RAD54*^{Sc}]
DNA helicase	*BLM*	*SGS1*^{Sc}, *rqh1*$^{+Sp}$
Growth factor signaling	*RAS*	*RAS1*^{Sc}, *RAS2*^{Sc}, *let-60*^{Ce}
	NF1	*IRA1*^{Sc}, *IRA2*^{Sc}
	MYC	*dMyc*^{Dm}
	PTH	*patched*^{Dm}
Cell cycle control	Cyclin D, Cyclin E	*CLN1*^{Sc}, *CLN2*^{Sc}, Cyclin D^{Rm}, Cyclin E^{Dm}
	P27^{kip1}	[*SIC1*^{Sc}]
	Rb	*Rbf*^{Dm}
Apoptosis	*BCL-2*	*ced-9*^{Ce}

Cell Cycle/DNA Damage Response Pathways

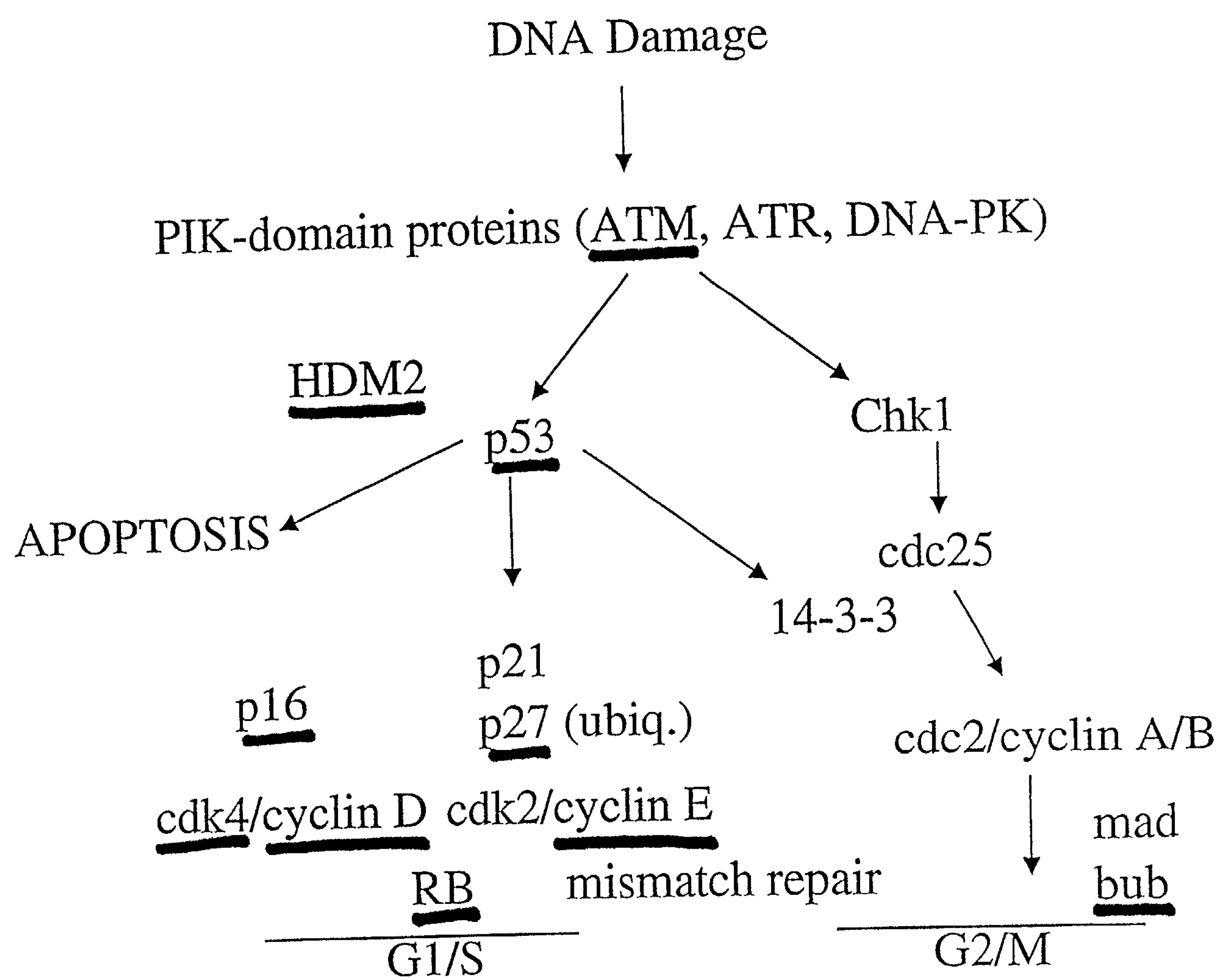
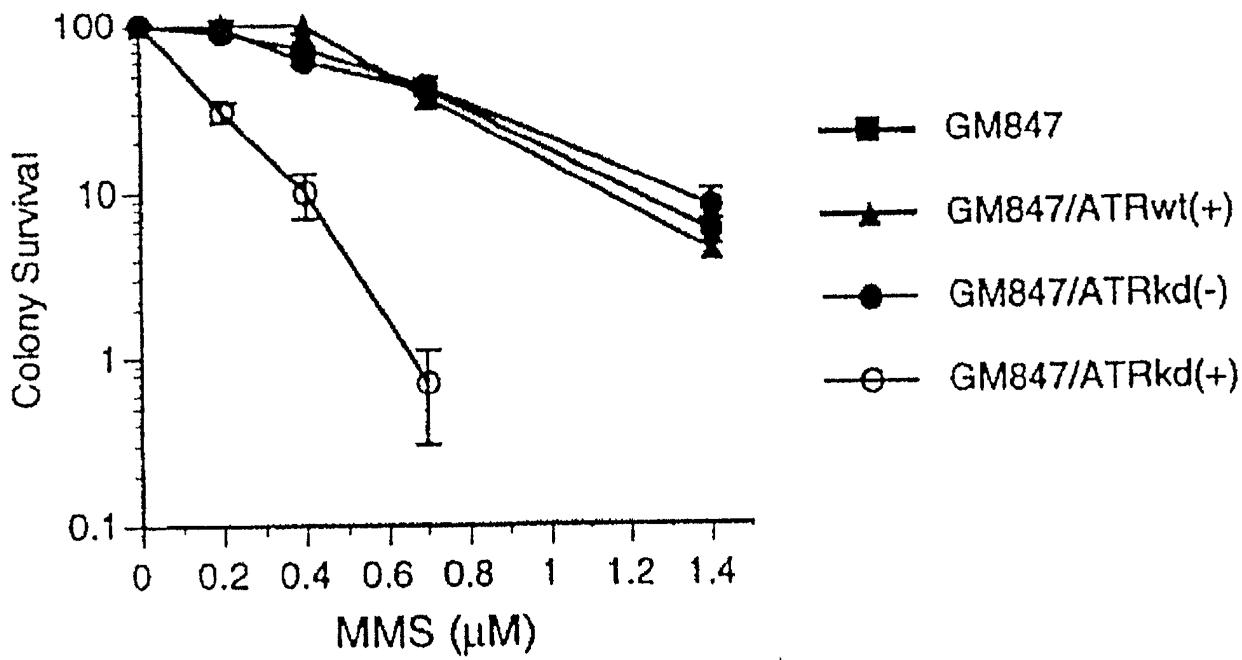


Figure 6

Figure 7


100
10
1
0.1
Colony Survival
0
0.2
0.4
0.6
0.8
1
1.2
1.4
MMS (µM)
GM847
GM847/ATRwt(+)
GM847/ATRkd(-)
GM847/ATRkd(+)